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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/677,733
Filing Date: October 01, 2003
Appellant(s): GARDNER ET AL.

Richard Aron Osman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 3, 2006 appealing from the Office action mailed September 5, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 1 and 2 under 35 USC 112, second paragraph, has been withdrawn. The rejection of claims 1

under 35 USC 103 is subject of the appeal. Claim 2 is objected to because it is dependent on rejected claim. It would be allowed if rewritten in an independent form with all the limitation of claim 1.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,843,683	EDERY et al.	12-1998
6,436,654	BERKENSTAM et al.	8-2002
6,291,429	TAKAHASKI et al.	9-2001
WO 97/18471	FESIK, S. W.	5-1997

(9) Grounds of Rejection

Claim 1 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Fesik (WO 97/18471) in view of any one of U. S. patents 5,843,683 (Edery *et al.*); 6,291,429 (Takahaski *et al.*); 6,436,654 (Berkenstam *et al.*).

Fesik teaches a method of identifying compounds that binds proteins using NMR methods, which include comparing the NMR of $^{1}H/^{15}N$ correlation spectra of ^{15}N labeled protein in the presence and absence of a potential compound that binds to said protein, see abstract and page 7, lines 29-32. They motivate one of ordinary skill in the art to use their method as they teach the many advantages of using their method, see page 8, line 8 to the end of the page. Also, they teach the application of their method to several proteins, see examples 1-2 and 4. Thus, the method is applicable to any protein of

interest. Fesik does not teach the application of his method to identify compound that bind or interact with PAS domain or proteins.

Edery *et al.* teach that abnormalities in PAS domain protein function may cause certain conditions or diseases in human, such as human behavior disorders and epithelial tissue cancer, see column 1, lines 41-55. Also, they teach that xenobiotics such the aryl hydrocarbon or dioxin complex (AH) with receptor containing PAS domain activates the metabolism of the xenobiotics in the liver and lungs of mammals, but the activation process produces gene products which are able to convert the xenobiotics to carcinogens, see column 2, lines 22-40. Thus, it appears that compounds that modulate the activity of the PAS domain would be useful in the prevention and treatment of disease, see column 3, lines 47-56.

Takahaski *et al.* teach the human and mouse genes and polypeptides component of the circadian clock (the clock polypeptide), which are member of the basic helix-loop-helix-PAS domain family of proteins, see column 7, lines 53-65. The polypeptide is thought to be involved in many regulatory functions in human, see column 16, line 8 through column 21, line 27. Also, Takahaski *et al.* teach that modulator of the clock polypeptide can be used for the identification of drugs for the treatment circadian rhythm dysfunctions, see column 9, lines 13-27.

Berkenstam *et al.* teach the various domains encompassed in human HIF-1α including PAS-B residues 178-390 of the human protein and its function, see column 7, last paragraph and column 8, lines 31-37 and column 11, lines 11-62. Also, they teach compounds that modulate the activity of various domains are potentially useful in the regulation of target genes normally associated with HIF-1α such as genes involved in angiogenesis, erythropoiesis, and glycolysis.

Each of Edery *et al.,* Takahaski *et al.* and Berkenstam *et al.* provide one of ordinary skill in the art with motivation to identify modulator of the PAS domains in various protein as they teach modulator of the PAS domain are potential drugs to

prevent and treat serious diseases. Fesik provide one of ordinary skill in the art with motivation to use their method to identify ligands for the PAS domains as they teach an easy method amenable to automation for identification of modulator of protein activity. Thus, it would have been obvious to one of ordinary skill in the art to use the method taught by Fesik to identify potential compound that modulate the activity of the PAS domain protein. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

(10) Response to Argument

Appellants' arguments and the declaration by Professor Stephen R. Sprang filed under 37 CFR 1.132 have been fully considered, but they are found unpersuasive. The claim is directed to a method of identifying foreign ligand to a PAS domain using the known NMR method taught by Fesik. The NMR method taught by Fesik is a general method applicable to any protein having any activity. It has no limit on the protein, or the presence or absence of cofactor required for the activity of said protein. Said method compares the $^{1}H/^{15}N$ correlation spectra of ^{15}N labeled protein in the presence and absence of a potential compound that binds to the protein. When an inhibitor binds specifically to a protein, a change in said NMR spectra is observed. The change can be in the form of small change in the observed chemical shifts of some residues, broadening of peak width, or a loss or appearance of a peak. The Fesik's method does not require NMR peak assignment to specific amino acid residues, any knowledge of the structure of the protein, or the amino acids of the ligand-binding cavity. The instant claim is directed to a method of using the Fesik's method to identify ligands for the PAS domain, which are also well known in the prior art. See Stephen R. Sprang declaration. The only requirement for the Fesik's method is a protein displaying activity. Evidence of record shows the PAS domains of the prior art are fully functional. The PAS domains taught by Ederly et al. is properly folded and under goes dimer formation and interacts with other PAS domains in solution. See examples 3 and 4. Berkenstam *et al.* teach the various domains encompassed in human HIF-1α including PAS-B residues 178-390

of the human protein, which displays activity in solution. See column 7, last paragraph and column 8, and claim 1. Since the PAS domains taught in the prior art are functional in solution, they must be properly folded with a hydrophobic core and preformed binding cavity or inducible binding cavity.

Appellants' focus their arguments on the limitation in the "wherein" clause, which states: the PAS domain is predetermined, prefolded, in its native state, and comprising a hydrophobic core that has no NMR-apparent a priori formed ligand cavity. Each of Edery *et al.,* Takahaski *et al.* and Berkenstam *et al.* teach a PAS domain having a binding activity in solution, and therefore, the PAS domains taught in the prior art must be predetermined, prefolded, in its native state, and comprising a hydrophobic core. The linear amino acid sequence contains all the information required for proper folding of the protein to predetermined three-dimensional structure including any binding cavity required for its activity. Proteins are known to instantaneously fold during their biosynthesis. All folded proteins have hydrophobic core otherwise the protein would not fold. The PAS domains of the prior art do not require any cofactor for their activity, but their activity requires binding another molecule. Thus, the PAS domains of the cited art must contain a binding cavity. The PAS domains are known to have specific biological function through interaction with other proteins and other molecules. The claim is not limited to a method of identifying a molecule that binds to a PAS domain in a specific binding cavity, or even the foreign ligand inhibits or interferes with the PAS domain activity. Also, the claim does not require that the predetermined domain must be recognized or in some other way acknowledged by some measurement prior to the practice of the method steps.

The fact that the NMR method cannot observe certain signals in the absence of a ligand does not mean that the ligand-binding site is not formed or is formed incompetently. The binding activities reported in the prior art are more sensitive and thus are able to observe the formation of the binding cavity. The major advantage of NMR techniques over the X-ray method is that it observes a protein molecule in its

native environment, i.e., in aqueous solution. Unlike crystals, protein molecules are neither static nor stationary in solution. Various protein molecules are constantly sampling different conformations and orientation relative to the magnetic field, i.e., tumbling in the magnetic field. If the changes are fast on the NMR experimental time scale, an average signal will appear for all the conformers and positions of the molecule relative to the magnetic field. If, however, the conformation changes are slow relative to the time scale, the NMR signals of some residues become much broader or not observable at all in many cases. Thus, one of ordinary skill in the art would not have been discouraged from using the Feisk's method because the presence or absence of some NMR peaks indicating the absence or presence of a ligand-binding site. The ordinary skill in the art would have known of the presence of the ligand-binding cavity because the protein has an activity in solution. There is no reason for one of ordinary skill in the art to carry out the monumental task of fully assigning all the ^{1}H, ^{13}C and ^{15}N NMR signals of a PAS domain to carry out the Feisk's for a PAS domain. The NMR signal due to residues involved in the interaction between the PAS domain and a foreign or native ligand can be identified in the presence of a ligand with relative ease by comparing the spectra in the presence and absence of the ligand. NMR signals for ^{1}H, ^{13}C and ^{15}N from amino acid residue in the binding cavity are perturbed the most in the presence of a ligand, and thus, can be identified and assigned with relative ease.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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